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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/519,990	01/04/2005	Nicoletta Bianchi	Q85654	3209

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SUGHRUE MION, PLLC
2100 PENNSYLVANIA AVENUE, N.W.
SUITE 800
WASHINGTON, DC 20037

EXAMINER	
GUDIBANDE, SATYANARAYAN R	

ART UNIT	PAPER NUMBER
1654	

MAIL DATE	DELIVERY MODE
07/08/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/519,990	BIANCHI ET AL.	
	Examiner	Art Unit	
	SATYANARAYANA R. GUDIBANDE	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of species rapamycin, and hydroxy urea in the reply filed on 12/22/06 was acknowledged and the traversal arguments were answered in a non-final action dated 2/6/07 and election/restriction made final.

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 4/14/08 has been entered.

Applicant's amendment to claims in the response filed on 2/19/08 has been acknowledged.

Claims 1-4 are pending.

Claims 1-4 are examined on the merit.

Any objections and rejections made in the previous office action dated 10/16/07 and not specifically mentioned here are considered withdrawn.

Maintained Rejections

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 3 and 4 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 3 and 4 recites the limitation "modifier of transcription process" in line 3. There is insufficient antecedent basis for this limitation in the claim.

Response to Arguments

Applicants state that amendment to claims 3 and 4 obviate the rejections.

Applicant's arguments filed 2/19/08 have been fully considered but they are not persuasive. The issue is the presence of the phrase "modifier of transcription process" as a limitation and this limitation has no antecedent basis in the base claims 1 or 2.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 remain rejected under 35 U.S.C. 102(a) as being anticipated by Johnston, et al., Blood, 98, 410 as stated in our office action dated 2/6/07 and as reiterated below. Response to applicant's remarks appear at the end of the reiterated rejection.

In the instant application, applicants claim a method of treating β-thalassaemia comprising administering a medicament comprising a pharmaceutically effective amount of rapamycin or a structural analog thereof to a patient in need of such treatment, wherein the β-thalassaemia is therapeutically treated by induction of HbF.

Johnston, et al., teaches a method of treatment for β-thalassaemia in a heterozygous murine model that carried deletions for both b1 (beta major) and b2 (beta minor) adult globin chains for thalassaemia. In the absence of a regulated expression the mouse model injected with AAV vectors expressing murine erythropoietin (epo) led to very high levels of serum epo and ultimate death of all model animals. However, the subsequent induction with rapamycin of AAV vectors expressing inducible epo led to a dose dependent increase in epo. It was also found that no detectable expression of epo in the absence of rapamycin and the induction was reversible. Thus the anemia associated with induced β-thalassaemia in this mouse model was treated with gene therapy wherein the gene expression was controlled by rapamycin. Therefore, the claim 1 is anticipated by the cited reference.

Response to Arguments

Applicants argue that the cited reference of Johnston "does not disclose, teach or suggest that rapamycin would be beneficial to thalassaemic patients as a HbF inducer, and therefore does not anticipate or render obvious present claim 1. Claim 1, as amended, is directed to a method of treating beta-thalassaemia comprising administering a medicament comprising a pharmaceutically effective amount of rapamycin or a structural analogue thereof to a patient in

need of such treatment, wherein the beta-thalassaemia is therapeutically treated by induction of HbF".

Further, applicants argue that, "As mentioned in the previous amendment filed August 6, 2007, the approach described by Johnston is relative to gene therapy. Specifically, Johnston describes a development of a gene therapy system based on inducible AAV vectors. The vectors carry a "therapeutic gene" (in the described case the erythropoietin gene, but the technology can be applied to many other genes) under the control of a transcription activation system. There is no teaching by Johnston that rapamycin would be useful to thalassaemic patients as a HbF inducer. Thus, Johnson does not disclose, teach or suggest all the limitations of claim 1 alone or in combination with Rachmilewitz".

Applicant's arguments filed 2/19/08 have been fully considered but they are not persuasive. Because, in the cited reference of Johnston, rapamycin was administered to a murine model for β-thalassaemia. Since rapamycin was administered to a mouse that exhibited β-thalassaemia, it is inherent property of administered rapamycin that treatment of β-thalassaemia is by induction of HbF.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-4 remain rejected under 35 U.S.C. 103(a) as being unpatentable over Johnston, et al., Blood, 2001, 98, 410 in view of Rachmilewitz, British Journal of Haematology, 1995, 91, 263-268 as stated in our non-final office action dated 2/6/07 and as reiterated below. Response to applicant's arguments appear at the end of the reiterated rejection.

In the instant application, applicants claim a method of treating β-thalassaemia comprising administering a medicament comprising a pharmaceutically effective amount of rapamycin or a structural analog thereof to a patient in need of such treatment, wherein the β-thalassaemia is therapeutically treated by induction of HbF. The method wherein the rapamycin or the structural analog is in combination with at least one modifier of a transcription process selected from the group consisting of cytosine arabinoside, retinoic acid, plicamycin, mithramycin, hydroxyurea, guanine, guanosine, triphosphate (GTP), gaunosine diphosphate (GDP) and guanosine monophosphate (GMP).

The reference of Johnston teaches a method of treatment for β-thalassaemia in a heterozygous murine model that carried deletions for both b1 (beta major) and b2 (beta minor)

adult globin chains for thalassaemia. In the absence of a regulated expression, the mouse model injected with AAV vectors expressing murine erythropoietin (epo) led to a very high levels of serum epo and ultimately caused the death of all model animals. However, the subsequent induction with rapamycin of AAV vectors expressing inducible epo led to a dose dependent increase in epo. It was also found that no detectable expression of epo in the absence of rapamycin and the induction was reversible. Thus the anemia associated with induced β-thalassaemia in this mouse model was treated with gene therapy wherein the gene expression was controlled by rapamycin. The treatment method of Johnston, et al., does not teach the combination with a modifier of a transcription process such as hydroxyurea.

Rachmilewitz teaches novel treatments for β-thalassaemia, which is a severe β-globin gene disorder. The β-thalassaemia disorders result in individuals who are homozygous for mutations (or deletions) in or around β-globin chain clusters (page 1, column 1, paragraph 1). The reference discloses that several agents are being studied for their ability to augment the post-natal synthesis of fetal haemoglobin (HbF) in patients with sickle cell and β-thalassaemia (page 263, column 2, paragraph 3) and hydroxyurea (HU) is the least toxic of several chemotherapeutic agents (page 264, column 1, paragraph 2). The HU reagent has been reported to be efficacious in patients with sickle-β-thalassaemia (page 265, column 1, paragraph 1). The reference also teaches that therapies based on the modulation of existing gene expression, given alone or in combination with other therapies, appear to offer significant promise in favorably modifying the clinical course of patients with sickle-cell disease and β-thalassaemia (page 266, column 2, paragraph 2). The reference further discloses that rHuEpo have been shown to augment HbF levels in erythroid cell culture and in experimental animals. On this basis rHuEpO has been used

in clinical trials and found to increase the percentage of F reticulocytes and HbF in sickle-cell patients when administered in high doses along with iron supplementation. Moreover, it seems that rHuEPO exerts an additive effect when given with HU in alternating doses. This is indicative of the fact that HU has been effective in a combination therapy with other agents in increasing the HbF levels in animal models (page 265, column 1, paragraph 2).

It would have been obvious to one of ordinary skill in the art to modify the teachings of Johnston and Rachmilewitz to develop a treatment method for β-thalassaemia by administering a medicament comprising a pharmaceutically effective amount of rapamycin and hydroxyurea, because, Johnston teaches the method of administering rapamycin to treat β-thalassaemia in murine models and Rachmilewitz teaches administration of hydroxyurea to treat β-thalassaemia. Rachmilewitz further teaches that rHuEpO has been used in clinical trials and it has been found to increase the percentage of F reticulocytes and HbF in sickle-cell patients when administered in high doses along with iron supplementation. According Rachmilewitz, it appears that rHuEPO exerts an additive effect when given with HU in alternating doses. According to MPEP. 2144.06, "It is prima facie obvious to combine two compositions each of which is taught by the prior art to be useful for the same purpose, in order to form a third composition to be used for the very same purpose.... [T]he idea of combining them flows logically from their having been individually taught in the prior art." In re Kerkhoven, 626 F.2d 846, 850, 205 USPQ 1069, 1072 (CCPA 1980), claims to a process of preparing a spray-dried detergent by mixing together two conventional spray-dried detergents were held to be prima facie obvious". The motivation to do so comes from the fact that such studies have been reported in the cited reference of Rachmilewitz wherein a controlled trial of recombinant human EPO (rHuEpo) and HU have

shown improvement in the quality and quantity of the newly formed red blood cells (RBC) compared to the use of each of the reagents alone (page 265, column 1, paragraph 3). The reference also states that therapies based on the modulation of existing gene expression, given alone or in combination with other therapies, appear to offer significant promise in favorably modifying the clinical course of patients with sickle-cell disease and β-thalassaemia (page 266, column 2, paragraph 2). There would have been reasonable expectation of success in a combination therapy given the fact such a therapy has been successfully been carried out as disclosed by Rachmilewitz as stated in earlier.

Therefore, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time of invention.

Response to Arguments

Applicants argue that the cited reference of Johnston "does not disclose, teach or suggest that rapamycin would be beneficial to thalassaemic patients as a HbF inducer, and therefore does not anticipate or render obvious present claim 1. Claim 1, as amended, is directed to a method of treating beta-thalassaemia comprising administering a medicament comprising a pharmaceutically effective amount of rapamycin or a structural analogue thereof to a patient in need of such treatment, wherein the beta-thalassaemia is therapeutically treated by induction of HbF".

Further, applicants argue that, "As mentioned in the previous amendment filed August 6, 2007, the approach described by Johnston is relative to gene therapy. Specifically, Johnston describes a development of a gene therapy system based on inducible AAV vectors. The vectors

carry a "therapeutic gene" (in the described case the erythropoietin gene, but the technology can be applied to many other genes) under the control of a transcription activation system. There is no teaching by Johnston that rapamycin would be useful to thalassaemic patients as a HbF inducer. Thus, Johnson does not disclose, teach or suggest all the limitations of claim 1 alone or in combination with Rachmilewitz".

Applicant's arguments filed 2/19/08 have been fully considered but they are not persuasive. Because, in the cited reference of Johnston, rapamycin was administered to a murine model for β-thalassaemia. Since rapamycin was administered to a mouse that exhibited β-thalassaemia, it is inherent property of administered rapamycin that treatment of β-thalassaemia is by induction of HbF. Further, the reference of Rachmilewitz teaches that HU reagent has been reported to be efficacious in patients with sickle-13-thalassaemia (page 265, column 1, paragraph 1). The reference also teaches that therapies based on the modulation of existing gene expression, **given alone or in combination with other therapies**, appear to offer significant promise in favorably modifying the clinical course of patients with sickle-cell disease and β-thalassaemia (page 266, column 2, paragraph 2) as stated in the office action dated 2/6/07. Therefore, combination of references Johnston and Rachmilewitz., teaches the instant invention and hence the invention as a whole is obvious to one of ordinary skill in the art at the time the invention was made.

New grounds of rejection

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-4 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In the instant application, applicants claim a method of treating β-thalassaemia comprising administering a medicament comprising a pharmaceutically effective amount of rapamycin or a structural analog thereof to a patient in need of such treatment, wherein the β-thalassaemia is therapeutically treated by induction of HbF.

In the instant invention, claims recite "rapamycin or a structural analogs thereof of rapamycin". The claim as recited encompasses any and all known and unknown structural analogs of rapamycin. The specification only provides the structure of rapamycin on page and incorporate by references the other structural analogs based on the reference of Dickman, 2000, Bioorganic and Medicinal Chemistry Letters, 10, 1405-1408. In examples 1 and 2 of the instant application, applicants discloses the use of only rapamycin and no other structural analogs of rapamycin to study the functional aspect of treating β-thalassaemia. According to the website: http://cancerweb.ncl.ac.uk/cgi-bin/omd?query=analog, analog is a compound structurally similar to another but not necessarily an isomer, for e.g., 5-fluorouracil is an analog of thymine (pages 4 and 5). Hence, structural similarity does not impart functional aspects to the analog molecules.

The MPEP clearly states that the purpose of the written description is to ensure that the inventor had possession of invention as of the filing date of the application, of the subject matter later claimed by him. An applicant shows possession of the claimed invention by describing the claimed invention with all of its limitations using such descriptive means as words, structures, figures, diagrams, and formulas that fully set forth the claimed invention. Lockwood v. American Airlines, Inc., 107 F.3d 1565, 1572, 41 USPQ2d 1961, 1966 (Fed. Cir.1997). The MPEP lists factors that can be used to determine if sufficient evidence of possession has been furnished in the disclosure of the application. These include, "level of skill and knowledge in the art, partial structure, physical and/or chemical properties, functional characteristics alone or coupled with a known or disclosed correlation between structure and function, and the method of making the claimed invention. Disclosure of any combination of such identifying characteristics that distinguish the claimed invention from other materials and would lead one of skill in the art to the conclusion that the applicant was in possession of the claimed invention is sufficient" MPEP 2163.

In the instant instance applicants have claimed structural analogs of rapamycin without providing the structural features of such analogs that would have same or similar functions to that of rapamycin. Use of only one compound (rapamycin) in the specific examples provided in the specification and recitation of unknown analogs of rapamycin in the claims without disclosing structural features and function associated with the structures indicates that the applicants are not in possession of the invention commensurate with the scope of the claim as recited.

Further, for a broad generic claim, the specification must provide adequate written description to identify the genus of the claim. In Regents of the University of California v. Eli Lilly & Co., the court stated: "A written description of an invention involving a chemical genus, like a description of a chemical species, 'requires a precise definition, such as by structure, formula, [or] chemical name,' of the claimed subject matter sufficient to distinguish it from other materials. Fiers, 984 F.2d at 1171, 25 USPQ2d at 1606; In re Smythe, 480 F.2d 1376, 1383, 178 USPQ 279, 284-85 (CCPA 1973) ("In other cases, particularly but not necessarily, chemical cases, where there is unpredictability in performance of certain species or subcombinations other than those specifically enumerated, one skilled in the art may be found not to have been placed in possession of a genus. . . ."). Regents of the University of California v. Eli Lilly & Co., 43 USPQ2d 1398.

Although, claim 2 recites three structural analogs such as: 7- (N-hydroxy)- acyl analogues, carbamoyl analogues and ureide analogues of rapamycin. The specification does not disclose the structural features of the same. the specification is also silent with respect to functional characteristics and efficacy of the compounds compared to rapamycin in treating β-thalassaemia. Thus, applicant's disclosure as originally submitted does not adequately support the claims as recited to commensurate with the scope of the claim as afore-described. Therefore, the claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) THE NAMES OF THE PARTIES TO A JOINT RESEARCH AGREEMENT.
(e) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC.
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.
(j) CLAIM OR CLAIMS (commencing on a separate sheet).
(k) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).
(l) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

The current specification lacks section b. The specification as disclosed does not divide the application into sections such as:
(f) BACKGROUND OF THE INVENTION.
    (1) Field of the Invention.
    (2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.
(g) BRIEF SUMMARY OF THE INVENTION.
(h) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).
(i) DETAILED DESCRIPTION OF THE INVENTION.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Satyanarayana R. Gudibande whose telephone number is 571-272-8146. The examiner can normally be reached on M-F 8-4.30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Cecilia Tsang can be reached on 571-272-0562. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Satyanarayana R Gudibande/
Examiner, Art Unit 1654

/Andrew D Kosar/
Primary Examiner, Art Unit 1654